2002-026246/03 B05 TANA 2000.04.28

TANABE SEIYAKU CO WO 200183460-A1

2000.04.28 2000-130371(+2000JP-130371) (2001.11.08) C07D 239/42, 401/12, 401/14, 403/04, 403/12, 405/14, 413/12, 413/14, 471/04, 498/04, 513/04

New cyclic compounds are phosphodiesterase V inhibitors for treating e.g. pulmonary hypertension and diabetes (Jpn)

C2002-007476 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW)

Addnl. Data: YAMADA K, MATSUKI K, OMORI K, KIKKAWA K 2001.03.15 2001WO-JP02034

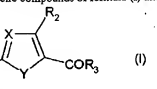
NOVELTY

Cyclic compounds (I) are new.

B(6-H, 7-H, 14-F1D, 14-F2B, 14-K1, 14-S4) .5

DETAILED DESCRIPTION

Cyclic compounds of formula (I) and their salts are new.



(I)

X = CH or N; pyridine

Y = NH, NR_4, S, O, CH=N, N=CH, N=N, CH=CH, CR_5 = N, CH=CR_6 or N=CR_7;

R_1 = CN or optionally substituted lower alkoxy, amino, Het, OH or QHet;

Het = nitrogenous heterocyclyl;

R_2 = optionally substituted arylamino, aryl-lower alkylamino, lower alkylamino, aryl-lower alkoxy, lower alkoxy, Het_1-lower alkoxy or heterocyclyl-lower alkylamino;

Het_1 = nitrogenous aromatic heterocyclyl;

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R_3 = optionally substituted aryl, Het, lower alkyl, lower alkoxy, cycloalkoxy, OHet or amino;

R_4-R_7 = optionally substituted aryl, Het, lower alkoxy or amino; or one of R_4-R_7 + R_3 = $NQCHQ_2CH_2O$;

Q = Me and

Q_2 = H or

Q + Q_2 = $(CH_2)_3$;

provided that when X = N, Y = CH=N or N=CH, R_2 = $NHCH_2Ar$, Ar = optionally substituted aryl, R_3 = optionally substituted alkyl or NHG and G = optionally substituted Het-lower alkyl, Het or lower cycloalkyl, then R_1 is not CN.

ACTIVITY

Cardiant; Antianginal; Hypotensive; Respiratory; Antidiabetic; Cardiovascular; Anorectic; Antiasthmatic.

No biological data is given.

MECHANISM OF ACTION

Phosphodiesterase-V inhibitor.

USE

Used for treating and preventing pulmonary hypertension and diabetes (claimed) as well as e.g. cardiac insufficiency, angina pectoris, hypertension, cardiovascular infarction and asthma.

ADMINISTRATION

Dosage is 0.01-100 (preferably 0.1-10) mg/kg/day.

EXAMPLE

Sodium hydride (60% in oil; 25 mg) was added to 2-(hydroxymethyl)pyridine (68 mg) in tetrahydrofuran (3 ml) and the mixture was stirred at room temperature for 30 minutes. 2-Chloro-5-(3,4,5-trimethoxyphenylcarbonyl)-4-(3-chloro-4-methoxybenzylaminopyrimidine (45 mg) in tetrahydrofuran (3 ml) was added and the mixture was stirred at room temperature for 1 hour. Work-up including silica gel chromatography (ethyl acetate:hexane:diisopropyl ether) gave 56.0 mg of 2-(2-pyridylmethoxy)-5-(3,4,5-trimethoxy phenylcarbonyl)-4-)-3-chloro-4-methoxybenzylamino)pyrimidine, m. pt. 129°C.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: Preparation of (I) comprises e.g. reacting a carboxylic acid derivative of formula (II) with RsH.

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(II)

(207pp2533DwgNo.0/0)

WO 200183460-A/2

1999-458431/38 B05 (B03) TANA 1998.01.20
TANABE SEIYAKU CO *WO 9936393-A1
1998.01.20 1998-071840(+1998US-071840) *(1999.07.22)* C07C 233/87, A61K 31/245, C07C 237/30, 311/09, C07D 333/34, 295/14, C07C 271/28, A61K 31/33

New alpha4-mediated cell adhesion inhibiting amide and thioamide compounds used to treat rheumatoid arthritis, etc. (Eng)

C1999-134597 N(AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW)

Addnl. Data: SIRCAR I, GUDMUNDSSON K S, MARTIN R
1999.01.19 1999WO-US00993

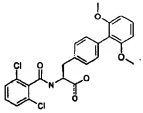
B(6-H, 7-H, 10-D2, 10-D3, 14-C3, 14-C9B, 14-E10, 14-E10C, 14-E11, 14-G2C, 14-K1, 14-K1A, 14-N4, 14-N13, 14-N17, 14-N17C, 14-S1, 14-S4) .10

NOVELTY

Hydrocarbyl- and heterocyclyl- amide and thioamide compounds (I) are new.

DETAILED DESCRIPTION

Hydrocarbyl- and heterocyclyl- amide and thioamide compounds (I) are new.



(Ia)

Ring A = an aromatic hydrocarbon ring or a heterocyclic ring;
Q = a bond, carbonyl, lower alkylene (optionally substituted by

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hydroxy or phenyl), lower alkenylene or O-(lower) alkylene;
n = 0-2;
W = O, S, CH=CH or N=CH;
Z' = O or S;
R^1-R^2 = H, halo, NO_2, CN, carboxyl or its amide or ester, lower alkylthio, lower alkanesulfonyl, hydroxy or lower alkyl, lower alkoxy, amino, sulfamoyl, aryl or heterocyclyl (all optionally substituted) or
two of R^1-R^5 = lower alkylenedioxy;
R^4 = tetrazolyl, carboxyl, an amide or its ester;
R^5 = H, nitro, hydroxyl, lower alkanoyl, lower alkoxy, halo, 2-oxopyrrolidinyl or amino or lower alkyl (both optionally substituted) and
R^6 = optionally substituted phenyl or heteroaryl,
provided that when Ring A = benzene, the ring is not substituted by methyl in the 3- and 5-positions or in the 2- and 4-positions.
An INDEPENDENT CLAIM is included for the preparation of (I).

ACTIVITY

Antiinflammatory.

MECHANISM OF ACTION

α_4-mediated cell adhesion inhibitor; $\alpha_4\beta_7$ mediated cell adhesion inhibitor; MadCAM-1 ligand-cell interaction inhibitor.
In a RPMI-CS-1 cell adhesion assay to measure the activity of (I) in inhibiting β_7-mediated cell adhesion, CS-1 derived peptide (CLHPGEILDVPST) and scrambled control peptide (CLHGPIELVSDPT) were used. N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine exhibited an IC_{50} value of upto 0.3 μM.

USE

Used to treat or prevent conditions caused by α4-mediated cell adhesion including rheumatoid arthritis, asthma, psoriasis, eczema, contact dermatitis and other skin inflammatory conditions, diabetes, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel disease (including ulcerative colitis and Crohn's disease) and other diseases involving leukocyte infiltration of the gastrointestinal tract or other epithelial-lined tissues such as the skin, urinary tract, respiratory airway and joint synovium (claimed).
(I) are also used to treat conditions involving leukocyte infiltration of other tissues including lung, blood vessels, heart and nervous system and transplanted organs such as the kidney, liver, pancreas and heart,

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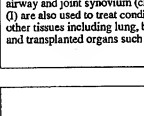
to inhibit interaction of a cell bearing a ligand of MadCAM-1 including $\alpha_4\beta_7$ integrins with MadCAM-1 or its extracellular domain and to treat pouchitis resulting after proctocolectomy and ileoanal anastomosis after irritable bowel disease, Celiac disease, nontropical Sprue, enteropathy associated with sero-negative arthropathies, lymphocytic and graft-versus-host disease, pancreatitis, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis and chronic inflammatory diseases of the lung that result in interstitial fibrosis (hypersensitivity pneumonitis, collagen disease and sarcoidosis).



(Ia)

ADVANTAGE

(I) have potential for fewer side-effects due to effects on other tissue types such as $\alpha_4\beta_1$ integrin.

SPECIFIC COMPOUNDS

14 Compounds (I) are specifically claimed e.g:
N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine (Ia).

ADMINISTRATION

The dosage is 0.1-100 (preferably 1-100) mg/kg/day orally or parenterally.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: (I) are prepared e.g. by:

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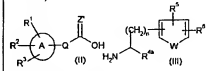
(1) condensing a compound of formula (II), its salt or reactive derivative with a compound of formula (III) or its salt;
(2) optionally converting the ester group into a carboxyl group and
(3) optionally converting the carboxyl group of the resulting compound into an ester, amide, tetrazolyl or salt to give (I; R^4 = R4a).



(II) (III)

R4a = an ester.
(243pp2419DwgNo.0/0)

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A1

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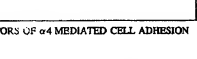
(54) Title: INHIBITORS OF α4 MEDIATED CELL ADHESION



(I)

(57) Abstract

The present invention relates to a pharmaceutical composition comprising as an active ingredient a compound of formula (I), wherein Ring A is an aromatic or a heterocyclic ring; Q is a bond, carbonyl, lower alkylene, lower alkenylene, –O–(lower alkylene)–, etc.; n is 0, 1 or 2; Z is oxygen or sulfur; W is oxygen, sulfur, –CH=CH–, –NH– or –N=CH–; R^1, R^2 and R^3 are the same or different and are hydrogen, halogen, hydroxyl, a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkoxy group, a substituted or unsubstituted amino group, etc.; R^4 is tetrazolyl, carboxyl group, amide or ester; R^5 is hydrogen, nitro, amino, hydroxyl, lower alkoxyl, lower alkyl, etc.; R^6 is selected from (a) a substituted or unsubstituted phenyl group, (b) a substituted or unsubstituted pyridyl group, (c) a substituted or unsubstituted thienyl group, (d) a substituted or unsubstituted benzofuranyl group, etc.; or a pharmaceutically acceptable salt thereof.